Design of multifunctional liposomal drug formulations for cancer therapy

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Abstract

Cancer remains a global health problem and a major cause of death worldwide. Statistical analysis published by the International Agency for Research on Cancer from the World Health Organization reveals that if the estimated trends continue, the incidence of all cancer cases will raise from 12.7 million new cases in 2008 to 21.2 million by 2030 [1]. Doxorubicin (DOX) is considered one of the main "first-line" anticancer drugs for a broad spectrum of tumor types, but this drug has the disadvantage of being toxic for other healthy organs and tissues. The use of liposomes as carriers of DOX is thus very appealing to counteract this disadvantage and protect the healthy tissues from contact with the DOX toxicity. Despite several liposomal formulations were already proposed for the delivery of DOX, the majority uses "active loading" methods and the small number of liposomal formulations that use "passive loading" methods achieve small encapsulation efficiency (EE) of the drug. The "active loading" methods are used to increase DOX amounts in the nanocarriers, but have however the disadvantage of drug precipitation and formation of dimers for which the therapeutic value is yet to be proved [2].

In this work it is proposed a nanocarrier system of Dioctadecyldimethylammonium Bromide (DODAB) and 1-oleoyl-rac-glycerol (Monoolein (MO)) (1:2) that has previously been studied as a system with great potentiality of encapsulating drugs, not only at the DODAB enriched bilayer level, but also at the inverted non-lamellar MO-enriched phases at the vesicle interior [3]. Therefore with this innovative polymorphic system the lipophylic area is greatly increased thus increasing the system capacity to increase the payload content even by a passive encapsulation.

Three methods of DOX passive encapsulation in the formulation DODAB:MO (1:2) were tested and characterized measuring the size and zeta potential of the liposomes overtime by dynamic and electrophoretic light scattering and measuring DOX EE (evaluated through UV/Vis spectrophotometry). EE studies revealed high encapsulation values of DOX (87 %) turning the developed formulation in a very promising nanocarrier system for DOX. The study of the partition coefficient of DOX has confirmed that it is highly distributed in the lipid formulation. The biophysical effects of DOX in the formulation indicated an increase in the cooperativity of the phase transition confirming DOX distribution at the membrane level. Furthermore, thermodynamical parameters of DOX partitioning indicated that the drug distribution in the lipid formulation occurred spontaneously. Cytotoxicity assays were also performed in a cancer cell line and it was concluded that the formulation with DOX encapsulated in DODAB:MO (1:2) has a better cytostatic effect than the free drug, confirming the potentiality of the developed formulation to be used in cancer treatment. Finally controlled release assays were carried out in media with different relevant physiological pH values (5 and 7.4) to predict the pharmacokinetic behavior of the drug when loaded in the developed nanocarriers..

Currently we are exploiting a distinct virtue of the co-delivery system, which is taking advantage of the positive charge of the nanocarrier to deveop hybrid co-delivery nanocarriers that combine chemotherapeutic agents with small interfering ribonucleic acids (siRNA targeted to MRP1 mRNA and siRNA targeted to BCL2 mRNA as suppressors of multidrug resistance).

References

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